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CASE REPORTS

Torsade de Pointes Induced by N-Acetylprocainamide

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N-Acetylprocainamide (NAPA), a class III antiarrhythmic drug, caused torsade de pointes in a 72 year old woman who had this arrhythmia on two previous occasions while being treated with quinidine and disopyramide. Initial evaluation with an intravenous infusion of NAPA indicated a favorable antiarrhythmic response. The QT_C interval was prolonged, but the 2.4 ms/μg per ml incremental QT_C interval lengthening caused by NAPA was not greater than usual. During subsequent oral therapy with NAPA, torsade de pointes developed at plasma levels of this drug that appeared to be well tolerated during the initial evaluation.

Torsade de pointes has been described as a complication of therapy with an increasing number of antiarrhythmic drugs and dramatically illustrates the potential of these agents to induce life-threatening ventricular arrhythmias (1–3). N-Acetylprocainamide (NAPA) is an active metabolite of procainamide, which was previously implicated as a cause of torsade de pointes in a patient who was being treated with procainamide and had a plasma procainamide level of 4.1 μg/ml (within the generally accepted therapeutic range) and a NAPA level of 32.8 μg/ml (4). We report on the first patient who developed this arrhythmia while receiving NAPA and demonstrate the potential of this drug to cause torsade de pointes.

Case Report

Because procainamide-induced lupus erythematosus may remit during NAPA therapy (5), a 72 year old woman with recurrent ventricular tachycardia and procainamide-induced lupus was hospitalized to evaluate her response to NAPA. She had a history of type II diabetes mellitus, angina pectoris and two myocardial infarctions within the past 5 years. She had recurrent polymorphic ventricular tachycardia and had been resuscitated three times while receiving either quinidine or disopyramide therapy. The first resuscitation did not occur while the patient was hospitalized. However, torsade de pointes was documented on the latter two occasions and was attributed to quinidine the first time and disopyramide the second. Just before these episodes, the QT_C interval of normal sinus rhythm and postextrasystolic beats averaged 0.56 and 0.61 second, respectively, when the patient was receiving quinidine, and 0.58 and 0.69 second, respectively, when the patient was receiving disopyramide. For 3 months before admission, she had been treated with procainamide (Procan SR), 500 mg every 6 hours, but had developed disabling stiffness and arthralgias in the joints of the hands, wrists, hips and knees. These symptoms were partially controlled with prednisone, 10 mg every other day. The patient was also being treated with digoxin, 0.25 mg/day, propranolol, 10 mg every 6 hours, insulin, furosemide, potassium chloride, aspirin and topical nitroglycerin.

Admission physical findings included a pulse rate of 80/min with frequent extrasystoles, a blood pressure of 160/80 mm Hg, a grade 2/6 systolic ejection murmur and an S_4 gallop rhythm. There was a minimal pretibial edema and peripheral pulses were decreased in both legs. Range of motion was decreased in the wrists, hands, hips and knees. The electrocardiogram showed frequent ventricular premature complexes, a QT_C interval of 0.45 second (normal 0.35 to 0.44) and left ventricular hypertrophy. Serum electrolytes were within normal limits. The antinuclear antibody titer was

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positive at a 1:10,240 dilution. Trough procainamide and NAPA plasma levels were 1.7 and 5.8 μg/ml, respectively. The trough plasma digoxin level was 1.3 ng/ml and the propranolol level was 9.0 ng/ml.

Methods

The research protocol for this investigation was approved by the Northwestern University Institutional Review Board on December 17, 1982. Informed consent was obtained using forms that were reviewed as a part of this protocol.

NAPA formulations and assay. The hydrochloride salt of NAPA was administered in a 100 mg/ml aqueous parenteral solution and as 500 mg tablets (American Critical Care). Plasma concentrations of procainamide and NAPA were measured by high performance liquid chromatography (6).

Electrocardiographic monitoring. The patient underwent on-line electrocardiographic monitoring during the entire study. The electrocardiogram was displayed on an oscilloscope, recorded on tape and simultaneously analyzed by a General Automation SPC-16/40 computer that was programmed to count the frequency of ventricular premature complexes during consecutive time intervals. After initial manual adjustment of recognition variables for each patient, this computer has been found to have a diagnostic accuracy of 94.4% with a 4.3% mean rate of false positive ventricular premature beat identification and a 2.3% mean rate of false negative identification (7). Episodes of ventricular tachycardia and torsade de pointes were identified by retrospective review of the electrocardiographic tape recording. QT intervals were measured manually from electrocardiographic tracings transcribed from the tapes at a paper speed of 25 mm/s. QT intervals were measured in 10 cycles and were averaged after applying the Bazett formula to correct for changes in heart rate (8).

Short-term antiarrhythmic testing and kinetic analysis. The patient's initial response to NAPA therapy was evaluated by a modification of a short-term testing procedure that has been developed for determining antiarrhythmic drug efficacy (9). A Sage pump was used to administer an initial 30 minute intravenous placebo infusion that was followed 30 minutes later by the infusion of 1.5 g of NAPA hydrochloride over a period of 30 minutes. Plasma NAPA concentrations produced by this intravenous infusion were analyzed with the SAAM 23 digital computer program developed by Berman and Weiss (10) and implemented on a Control Data Corporation Cyber 170/730 computer. The disposition kinetics of NAPA were modeled with a three compartment, open mammillary system with elimination from the central compartment. The relation between estimated biophase concentrations of NAPA and QT_C interval prolongation was analyzed with a linear effect model, similar to that previously used to study the vasodilator- and ganglionic-blocking actions of this drug (11). The results of this analysis and NAPA plasma concentrations measured during subsequent therapy with the oral formulation of this drug were then used to calculate expected QT_C intervals that could then be compared with the actual values. An E_{MAX} model was used to analyze the relation between ventricular premature beat frequency and NAPA concentrations in this biophase compartment (12).

Results

Initial evaluation. Four episodes of nonsustained ventricular tachycardia (< 10 consecutive beats) were observed during the first 8 hours after admission, and ventricular premature beat frequency averaged 5.4/min. Procainamide was then discontinued and the patient was observed without receiving antiarrhythmic therapy for the next 18 hours. During this time, plasma procainamide and NAPA levels decreased to 0.4 and 3.4 μg/ml, respectively, and the patient had 14 episodes of nonsustained multiform ventricular tachycardia at a rate as high as 140 beats/min. Ventricular premature beat frequency averaged 6.4/min during the last 8 hours of this period.

Response to intravenous NAPA infusion. The intravenous infusion produced peak plasma NAPA levels of 36.3 μg/ml and was accompanied by the changes in ectopic beat frequency and QT_C intervals shown in Figure 1. There were three episodes of three to four beat ventricular tachycardia (maximal rate = 182 beats/min) during the first 15 minutes after the intravenous infusion was completed, but then none occurred for 13 hours. The infusion was well tolerated, although mean arterial pressure decreased from 93 mm Hg during the placebo period to a minimum of 73 mm Hg 5 minutes after the infusion was completed. Pharmacokinetic analysis indicated that the elimination half-life and clearance of NAPA were 8.1 hours and 139.6 ml/min, respectively, and that the steady state distribution volume was 106 liters or 1.2 liters/kg. Analysis of drug-induced prolongation of QT_C interval indicated that this interval was prolonged by 2.4 ms for every 1 μg/ml increment in biophase NAPA concentration. The rate constants for NAPA entry and exit from the hypothetical biophase compartment were 0.020 and 0.161 min^{-1}, respectively, so that maximal QT_C interval prolongation would be expected 14.7 minutes after bolus intravenous injection. Intrinsic variability in the frequency of ventricular premature beats precluded rigorous correlation of changes in ectopic beat frequency with NAPA plasma levels during the entire study period. However, analysis of observations made during the placebo period and the first 4 hours after NAPA infusion suggested that this drug suppressed ventricular premature beats in a dose-dependent manner and that a NAPA plasma concentration of 8.5 μg/ml would effect half maximal suppression.

Because of this favorable response to short-term antiar-

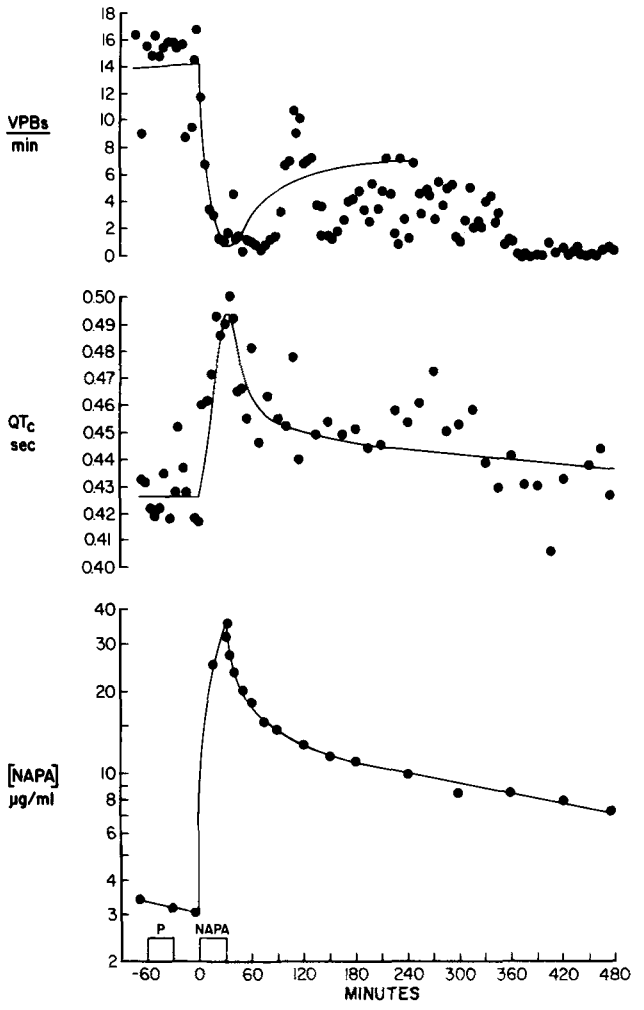


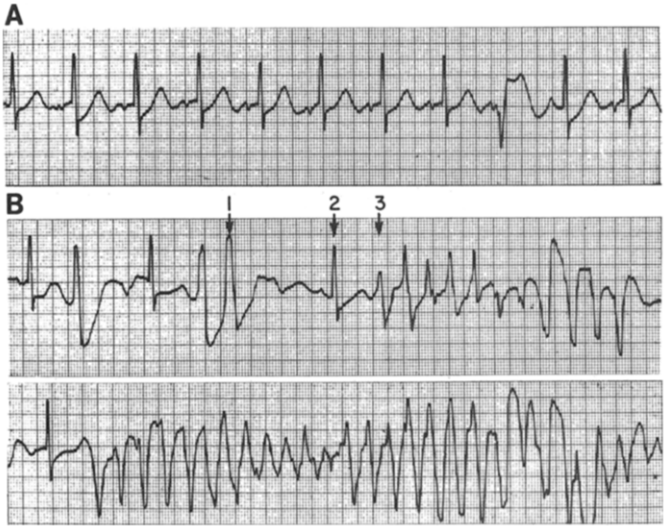
Figure 1. Initial evaluation of the patient's response to NAPA. Half an hour after a 30 minute placebo infusion (P), NAPA was infused intravenously over 30 minutes. Plasma NAPA concentrations (**bottom panel**) were used for kinetic analysis of concentration-related changes in QT_C interval (**middle panel**) and ventricular premature beat frequency (VPBs/min) (**top panel**). The QT_C interval averaged 0.43 second during the placebo period and reached a maximal value of 0.50 second shortly after the NAPA infusion was stopped; respective values of QT were 0.38 and 0.45 second.

rhythmic testing, the patient was started on oral therapy with a NAPA dose of 1.5 g every 8 hours, which was expected to provide mean plasma NAPA concentrations of approximately 20 μg/ml. Ectopic ventricular premature beat frequency averaged 4.4/min during the first two dosing intervals. Evaluation at that time indicated the return of episodic nonsustained ventricular tachycardia with a maximal rate of 205 beats/min. The trough NAPA level was 14.0 μg/ml and the QT_C of 0.45 second was close to the value of 0.46 second estimated from the kinetic analysis.

Development of torsade de pointes. We attempted to suppress the nonsustained ventricular tachycardia by increasing the NAPA dose to 2.0 g every 8 hours. Three hours later, the patient developed torsade de pointes (Fig. 2) that degenerated into ventricular fibrillation requiring direct current cardioversion and lidocaine therapy. At this time, the plasma NAPA level was 32.4 μg/ml. The expected QT_C interval of 0.49 second agreed closely with the value of 0.50 second measured during intervals of normal sinus rhythm 15 minutes before this episode. However, the QT_C interval of the normal beats and the postextrasystolic beat that immediately preceded the torsade de pointes were 0.53 and 0.60 second, respectively. Serum potassium, calcium and magnesium concentrations were 4.3 mEq/liter, 7.6 mg/dl and 2.2 mg/dl, respectively.

Follow-up. The patient was subsequently withdrawn from lidocaine therapy and consented to invasive studies that she had previously refused. Ventricular tachycardia could not be induced by programmed electrical stimulation with ventricular burst pacing and S_1, S_2 and S_3 stimuli at multiple cycle lengths applied to right ventricular apical and outflow sites. A gated pool scan demonstrated a large dyskinetic area and a possible apical aneurysm in the left ventricle. Although the patient continued to have frequent ventricular premature beats and spontaneous episodes of nonsustained ventricular tachycardia, the QT_C interval of normal beats was 0.43 second and that of postextrasystolic beats was 0.47 second; she was discharged from the hospital without further antiarrhythmic therapy. For 5 months since discharge, she has not had symptomatic ventricular tachycardia.

Figure 2. Modified electrocardiogram of lead V_1 obtained several seconds before (**A**) and during (**B**) the episode of NAPA-induced torsade de pointes that required cardioversion. The normal sinus beats in **A** have a QT_C interval of 0.53 second (QT = 0.48 second). The sequence leading to this arrhythmia (**B**) began when a premature ventricular beat (**arrow 1**) was followed by a long compensatory pause that was ended by a supraventricular beat (**arrow 2**) that had a QT_C interval of 0.60 second (QT = 0.54 second). The subsequent ventricular premature beat (**arrow 3**) had a coupling interval of 0.62 second and initiated ventricular tachycardia.



Discussion

Torsade de pointes most commonly results from drug therapy, and class I antiarrhythmic agents have been implicated most frequently (1–3). Recent reports indicate that this arrhythmia can be caused by amiodarone, a class III antiarrhythmic drug (13). N-Acetylprocainamide, NAPA, belongs to this antiarrhythmic class, because its primary electrophysiologic action is to prolong action potential duration (14).

Characteristics of this episode of torsade de pointes. Torsade de pointes is thought to be a reentrant arrhythmia that arises from inhomogeneous repolarization of neighboring areas of myocardium (15). The QT interval is prolonged, usually exceeding 0.60 second immediately before the onset of this arrhythmia (2,3), and the arrhythmia is initiated by a ventricular premature beat with a coupling interval ranging from 0.44 to 0.68 second (3). It has recently been shown (16) that the ventricular beats immediately preceding the onset of torsade de pointes exhibit a long-short cycle sequence. The episode of torsade de pointes shown in Figure 2 exhibits these features, as well as the changing ventricular complex configuration that is characteristic of this arrhythmia.

Fallibility of short-term antiarrhythmic testing. Potential aggravation of ventricular arrhythmias by antiarrhythmic drugs constitutes a major rationale for systematic initial drug testing before beginning long-term antiarrhythmic therapy (17). However, our patient demonstrated an apparently favorable response to an initial intravenous infusion of NAPA that encompassed plasma levels that later caused torsade de pointes. During this evaluation, QT intervals were prolonged. This prolongation primarily reflected the patient's relatively long baseline QT interval, because the incremental prolongation associated with NAPA therapy was no greater than that reported in patients (18) who subsequently tolerated long-term therapy with NAPA levels as high as 30 to 50 μg/ml (19). Hypokalemia and hypomagnesemia are commonly present when patients develop torsade de pointes despite normal plasma levels of antiarrhythmic drugs (16), but were excluded as contributory factors in our patient. Although we cannot explain why torsade de pointes subsequently developed at NAPA plasma levels that initially appeared to be well tolerated, it is clear that response to short-term antiarrhythmic drug testing may not always predict subsequent therapeutic outcome.

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